Penicillin Resistance Not a Factor in Outcome from Invasive *Streptococcus pneumoniae* Community-Acquired Pneumonia in Adults When Appropriate Empiric Therapy Is Started

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ABSTRACT: *Background:* Invasive *Streptococcus pneumoniae* pneumonia among adults due to penicillin-resistant or intermediate resistant strains was investigated to determine whether these patients responded poorly to common antibiotic regimens compared to pneumonia due to susceptible strains. *Methods:* During a 21-year period (1983–2003), clinical outcome was analyzed among 3 groups of adults, 19 with resistant, 33 with intermediate, and 133 with susceptible invasive *S pneumoniae* pneumonia admitted to hospitals in Huntington, West Virginia. Adults with resistant and intermediate infections were matched by age and month of admission to a group of 133 adults with penicillin-susceptible infections. All isolates of resistant and intermediate infections were capsular serotypes/serogroups 6, 9, 14, 19, and 23, and isolates of susceptible infections included 24 different serotypes/serogroups. Case fatality rates were calculated for deaths that occurred during the first 7, first 14, and first 21 days of hospitalization. Minimal inhibitory concentration (MIC) was determined by E-test and capsular serotype by Quellung procedures. *Results:* The resistant and susceptible groups did not differ in several measures of severity of illness, including admission vital signs, duration of fever, mean total leukocyte count, number of lobes involved, preexisting underlying diseases, and antibiotic treatment regimens. There were no significant differences in case fatality rates between the 3 groups of pneumonia by days in hospital, age, severity of illness, and empiric antibiotic treatment regimen with a cephalosporin and a macrolide, the most common antibiotic regimen. *Conclusions:* These findings provide evidence that combination antibiotic regimens effective in the treatment of invasive susceptible *S pneumoniae* pneumonia are equally effective in the treatment of invasive resistant (MIC = 2–4 μg/mL) and of intermediate (MIC = 0.1–1 μg/mL) *S pneumoniae* pneumonia. **KEY INDEXING TERMS:** Penicillin-resistant *Streptococcus pneumoniae*; Pneumococcal pneumonia; Case fatality rate; Bacteremia; Penicillin sensitive *Streptococcus pneumoniae*. **[Am J Med Sci 2007;333(3):161–167.]**

Streptococcus pneumoniae is the most common cause of community-acquired pneumonia (CAP) among adults, and invasive *S pneumoniae* pneumonia represents serious disease with high case fatality rates that range between 10% and 20% and approach 35% in the elderly.[1–4] The past 3 decades ushered in the emergence and spread worldwide of penicillin-nonsusceptible *S pneumoniae* (PNSP), which poses a new challenge to antibiotic management of invasive *S pneumoniae* pneumonia due to PNSP.[5–7] Several studies have shown that the clinical outcome of patients receiving a penicillin treatment for invasive *S pneumoniae* pneumonia is not affected by the presence of intermediate susceptibility to penicillin (PISP) (minimal inhibitory concentration [MIC] = 0.1–1 μg/mL).[8–11]

Few data are available on the clinical outcome of CAP due to invasive high resistant *S pneumoniae* (PRSP) isolates (MIC ≥2 μg/mL) among adults treated with empiric antibiotic regimens recommended by expert guidelines.[12,13] The emergence of penicillin resistance among *S pneumoniae* raised concerns that PRSP infections would not respond well to the antibiotic regimens usually used in the

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treatment of invasive *S pneumoniae* CAP caused by PISP and penicillin susceptible (PSSP) (MIC ≤0.06 μg/mL) strains. Clinical outcome was investigated among a group of adults with invasive *S pneumoniae* CAP infected with PRSP (MIC = 2–4 μg/mL) compared to PISP and PSSP to determine whether resistance was a key factor in a fatal outcome.

Materials and Methods

Patient Population

In this retrospective study, the clinical features and outcome were analyzed of all 52 adults with CAP due to invasive PNSP (19 PRSP and 33 PISP) admitted to the 3 hospitals in Huntington, West Virginia, affiliated with the Marshall University Joan C. Edward School of Medicine between July 1, 1983 and June 30, 2003.[2,5,9] All patients had CAP; the diagnosis of invasive pneumonia was based on radiographic evidence of pneumonia on chest radiograph and a blood culture positive for *Streptococcus pneumoniae* obtained on admission to the hospital. The group of patients with invasive PNSP pneumonia was matched by age and date of admission to a group of 133 patients admitted to the same hospitals with invasive PSSP pneumonia. The 2 groups did not differ significantly for admission clinical and laboratory findings and underlying diseases (Table 1). None of the patients had nosocomial pneumonia.

About 300,000 persons reside in the Huntington metropolitan area, which includes the City of Huntington and several surrounding counties of southern West Virginia and the neighboring counties of eastern Kentucky and southern Ohio. Three hospitals in Huntington serve this area, namely Cabell Huntington Hospital (300 beds), St. Mary's Hospital (400 beds), and the Veterans Administration Medical Center (150 beds). They are the only hospitals in Huntington and the adjacent counties in West Virginia.

Streptococcus pneumoniae *Isolates*

All isolates except 2 were recovered from blood cultures and those 2 were recovered from pleural fluid submitted to the microbiology laboratories of the 3 Huntington hospitals and were provided to us through the cooperation of individual microbiology laboratory staffs. Isolates were transported to our research laboratory on trypticase soy agar supplemented with 5% sheep blood and stored frozen at −70°C in glycerol/brain heart infusion broth media. They were tested either fresh or from frozen storage by being quickly thawed in a 36°C water bath and twice passaged overnight at 35°C in 5% CO_2 atmosphere on trypticase soy agar supplemented with 5% sheep blood (Remel, Lenexa, Kansas). The inoculum dose was obtained by seeding 1 mL of sterile broth with several colonies of an overnight culture to the equivalent of 0.5 McFarland Standard. Capsular serotyping (Quellung reaction) was done on fresh isolates using type-specific anticapsular antibody obtained from the Statens Serum Institute (Copenhagen, Denmark).[2]

Susceptibility Tests

The penicillin MIC of each isolate was determined using the Etest (AB Biodisk), and CLSI interpretive standards were used to categorize susceptibility and resistance to penicillin.[14] The MIC level for PSSP isolates was ≤0.06 μg/mL; PISP isolates was 0.1–1 μg/mL; and, PRSP isolates was ≥2 μg/mL. No PRSP isolate had an MIC greater than 4 μg/mL. Isolates that exhibited a borderline result were tested 3 times to ensure accuracy. All PISP and PRSP isolates were tested for MIC using the Etest (AB Biodisk) to cefaclor, cefuroxime, cefotaxime, and imipenem. All PSSP, PISP, and PRSP isolates were tested against the panel of antibiotics specified by CLSI using the Kirby-Bauer disk diffusion method, including ofloxacin (5 μg), erythromycin (15 μg), tetracycline (30 μg), chloramphenicol (30 μg), trimethoprim/sulfamethoxazole (1.25 μg/23.75 μg), and vancomycin (30 μg).

Table 1. Attributes of Patients with Susceptible or Resistant Invasive *Streptococcus pneumoniae* Community-Acquired Pneumonia

Attributes	Patients with Resistant Infection[a] (n = 52)	Patients with Susceptible Infection (n = 133)	*P*-Value (Statistical Test)
Age in years (avg)	66	65	0.73 (2-tailed, *t*-test)
Admission vital signs			
Temperature (avg)	37.5°C (99.6°F)	37.2°C (99.0°F)	0.65 (2-tailed, *t*-test)
Pulse (avg)	107 beats/min	108 beats/min	0.66 (2-tailed, *t*-test)
Respiratory rate (avg)	26/min	27/min	0.50 (2-tailed, *t*-test)
Systolic blood pressure (avg)	118 mm Hg	120 mm Hg	0.74 (2-tailed, *t*-test)
Number with <90 mm Hg	6 (11.5%)	14 (10.4%)	$\chi^2 = 0.00$, df = 1, $P = 1.00$
Total leukocyte count (Avg.)	18,210/mm^3	16,587/mm^3	0.39 (2-tailed, t-test)
Number of lobes involved, n (%)			
1	32 (61.5)	72 (54.5)	$\chi^2 = 1.48$
2	17 (32.7)	51 (38.1)	df = 3
3	3 (5.8)	8 (6.0)	<1.00
4	0	2 (1.5)	
Underlying diseases: n (%)			
ASHD	17 (32.7)	38 (28.6)	0.60[b]
Cancer, any	13 (25.0)	28 (20.9)	0.70[b]
Alcoholism, chronic	8 (15.4)	19 (14.3)	1.00[b]
Diabetes mellitus	15 (28.8)	35 (26.3)	0.85[b]
Chronic renal disease	3 (5.8)	12 (9.0)	0.56[b]
COPD	21 (40.4)	62 (46.3)	0.44[b]
Essential hypertension	20 (38.5)	54 (40.6)	0.87[b]
Splenectomy	2 (3.8)	3 (2.2)	0.62[b]

[a] *Resistant infection includes all Streptococcus pneumoniae isolates with an MIC of 0.1–4 μg/mL.*
[b] *Fisher exact test, 2-tailed.*
ASHD, arteriosclerotic heart disease; COPD, chronic obstructive pulmonary disease.